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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/042,775	01/08/2002	Richard A. Gatti	UC081.001A	5310

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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 03/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/042,775	GATTI ET AL.	
	Examiner	Art Unit	
	Maria B Marvich, PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-7,9-19,21 and 23-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,6,10-19,21 and 23-27* is/are rejected.

7)☒ Claim(s) *7 and 9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/2/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to an amendment filed 12/1/03. Claims 4, 8, 20 and 22 have been canceled. Claims 1-3, 7, 9-10, 17-18, 21 and 23 have been amended. Claims 1-3, 5-7, 9-19, 21 and 23-27 are pending. An IDS filed 7/2/03 has been identified and considered. The signed and initialed PTO Form 1449 has been mailed with this action. There are new grounds of rejection herein and therefore this rejection is not final.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 3 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. **This is a new rejection.**

Applicants claim a genus of variola viral vectors.

The written description requirement for genus claims may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with known or disclosed

correlations between function and structure, or by a combination of such characteristics sufficient to show that the applicant was in possession of the claimed genus.

In the instant case, applicants recite that for expression of ATM protein, a variola viral vector is to be used. Applicants teach that vaccinia is a member of the variola virus family and disclose that vaccinia is used to express ATM (see page 7, last paragraph). The prior art teaches that variola virus and vaccinia virus belong to the Poxviridae family and are members of the Orthopoxvirus genera (page 1165, Fundamental Virology, Third Edition). Neither applicant nor the prior art teach use of variola virus as a vector for the expression of heterologous proteins. Given that neither the prior art nor applicants have described a specific variola viral vector or how to generate a variola viral vector to express a heterologous protein in mammalian cells, it is concluded that the invention must be empirically determined. In an unpredictable art, the disclosure of no species would not represent to the skilled artisan a representative number of species sufficient to show applicants were in possession of claimed genus.

Claim 7 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new rejection. This is a new matter rejection.**

Claim 7 recites the limitation that "said ATM-deficient mammalian cells are ATM deficient". Neither the specification nor the prior art, indicate that HeLa cells are by nature ATM deficient. The disclosure does not teach that the HeLa cells are altered to become ATM

deficient. Therefore, the disclosure does not provide literal support for the inclusion of the limitation that the HeLa cells are ATM deficient.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This is a new rejection.**

Claim 3 is vague and indefinite in that the metes and bounds of a "variola viral vector" are unclear. A variola viral vector for the expression of heterologous proteins is not known in the art nor does the specification teach generation or use of a variola viral vector for the expression of ATM. While the specification teaches that vaccinia virus is a member of the variola virus family, the prior art teaches that variola virus and vaccinia virus are members of the Poxviridae family and of the Orthopoxvirus genera (page 1165, Fundamental Virology, Third Edition). Therefore, it is unclear what is or constitutes a variola virus vector for heterologous expression of ATM.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2, 6, 10, 12-13 and 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kastan et al. (US 6,387,640 B1 see entire document) in view of Rappold et al (JCB Vol 153(3), pp 613-620, see entire document). **This rejection is maintained for reasons of record in the office action filed 8/29/03 and restated below. Upon reconsideration, this rejection has been extended to claims 10, 14-16 and 23-27.**

Applicants claim a method for recombinant production of functional ataxia-telangiectasis (ATM) protein by infecting ATM-deficient mammalian cells with a viral vector encoding ATM under control of a promoter that is a synthetic early/late viral promoter.

Kastan et al. teach vectors for the cloning and expression of ATM kinase or FLAG-tagged ATM kinase (column 19, line 32-35). A wide variety of promoters are contemplated (e.g. column 20, line 1-23). Preferred vectors are viral vectors such as vaccinia (column 20, line 25-29). Methods for expression of ATM *in vivo* in a cell are provided (e.g. column 28, line 25-32 or column 30, line 56-column 31, line 33). FLAG tag is utilized for immunoprecipitation of ATM with M2 monoclonal antibody following transfection of 293T cells with a cloned chimeric FLAG-ATM gene (column 31, line 2-22). Kastan et al. teach that tumor cells such as MCF7 and RKO cells represent an example of a mammalian expression cells (column 19, line 63-67) that can be used for functional assays of ATM activity such as phosphorylation of p53 (column 31, line 42-44). Kastan et al. do not teach use of ATM deficient cells for ATM expression.

Rappold et al teach that an examination of ATM function is hampered in wild-type cells (page 615, column 1, paragraph 2). They further teach that to examine the effects of radiation on cells, they must use ATM deficient cells. Specifically, they use a fibroblast cell line that is

devoid of ATM called FT169A (page 615, column 1, paragraph 3). In these experiments, FT169A cells express no ATM until reconstituted with wild-type ATM cDNA, YZ5 (e.g. Figure 3A). Therefore, expression of ATM in FT169A results in regain of function.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the tumor cells taught by Kastan et al. with the ATM deficient cells taught by Rappold et al. because Kastan et al. teach that it is within the ordinary skill of the art to express recombinant ATM in a cell and because Rappold et al. teach that it is within the ordinary skill of the art to use an ATM deficient cell as a host cell for expression. One would have been motivated to do so in order to receive the expected benefit of unhampered comparison of functional assays involving the analysis of ATM kinase activity. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 1-2, 6, 10-11 and 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kastan et al. US 6,387,640 B1 (see entire document) in view of Zhang et al (PNAS 94, pp 8021-8026, see entire document). **This rejection is maintained for reasons of record in the office action filed 8/29/03 and restated below. Upon reconsideration, this rejection has been extended to claims 10, 14 and 23-27.**

Applicants claim a method for recombinant production of functional ataxia-telangiectasis (ATM) protein by infecting ATM-deficient mammalian cells with a viral vector encoding ataxia-telangiectasia protein and isolating with anti-ATM antibody.

Kastan et al. teach expression vectors for expression of ATM kinase or Flag tagged ATM kinase (column 19, line 32-35). A wide variety of promoters are contemplated (e.g. column 20, line 1-23). Preferred vectors are viral vectors such as vaccinia (column 20, line 25-29). Methods for expression of ATM in vivo in a cell are provided (e.g. column 28, line 25-32 or column 30, line 56-column 31, line 33). FLAG tag is utilized for immunoprecipitation of ATM with M2 monoclonal antibody following transfection of 293T cells with a cloned ATM gene (column 31, line 2-22). Kastan et al. teach that tumor cells such as MCF7 and RKO cells represent an example of a mammalian expression cells (column 19, line 63-67) that can be used for functional assays of ATM activity such as phosphorylation of p53 (column 31, line 42-44). Kastan et al. do not teach infection of ATM deficient cells nor does Kastan et al. teach use of anti-ATM for isolation of ATM.

Zhang et al teach expression of ATM in ATM deficient cells to avoid isolation of endogenous ATM (e.g. page 8023, column 2). Three anti-ATM antibodies were used to isolate ATM in AT1ABR and AT3ABR cells which express no endogenous ATM (e.g. Figure 2). ATM was expressed from an EBV based vector to complement radiosensitive phenotypes and to complement defective phosphorylation of p21/WAF in these cells (e.g. Figure 5). Therefore, expression of ATM in AT1ABR and AT3ABR cells results in regain of function.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the tumor cells and the FLAG antibody taught by Kastan et al. with the ATM deficient cells and anti-ATM antibodies taught by Zhang et al because Kastan et al teach that it is within the ordinary skill of the art to express recombinant ATM in a cell and isolate it with anti-FLAG and because Zhang et al teach that it is within the ordinary skill of the art to use

an ATM deficient cell as a host cell for expression and to isolate ATM with anti-ATM. One would have been motivated to do so in order to receive the expected benefit of detection of any endogenous ATM in the cell by use of anti-ATM and not FLAG that detects recombinant ATM and the avoidance of isolation of endogenous ATM by use of an ATM deficient cell line. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claim 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kastan et al. (US 6,387,640 B1 see entire document) and Rappold et al (JCB Vol 153(3), pp 613-620, see entire document) or Zhang et al (PNAS 94, pp 8021-8026, see entire document) in view of Chakrabarti et al (Biotechniques Vol 23 (6), pp 1094-1097, see entire document). **This is a new rejection.**

Applicants claim a method for recombinant production of functional ataxia-telangiectasis (ATM) protein by infecting ATM-deficient mammalian cells with a viral vector encoding ATM under control of a promoter that is a synthetic early/late viral promoter.

The teachings of Kastan et al and Rappold et al or Zhang et al are described above and are applied as before except that neither Kastan et al or Rappold et al or Zhang et al teach use of a synthetic early/late viral promoter.

Chakrabarti et al teach use of a compact synthetic vaccinia virus early/late promoter for protein expression. A compact promoter was designed to overcome the obstacle s of size limitations in viral vectors. By utilizing a smaller promoter that is sufficient for expression of heterologous sequences, larger coding sequences can be employed. In order to generate a

compact promoter, the early and late promoters are overlapping. The strength of the resulting promoter was found to be stronger than that a variety of naturally occurring viral promoters (see e.g. table 1).

It would have been obvious to one of ordinary skill in the art at the time the invention was made it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the synthetic promoter taught by Chakrabarti et al with that of Kastan et al because Kastan et al that it is within ordinary skill of the art to use any promoter or regulatory sequence to express ATM and because Chakrabarti et al teach that it is within the ordinary skill of the art to express heterologous proteins using the synthetic vaccinia early late/ promoter. One would have been motivated to do so in order to receive the expected benefit of that the use of the compact synthetic promoter allows larger coding sequences to be expressed. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Arguments

Applicants state on page 7 of the amendment filed 12/1/03 that the amended claim clarifies that HeLa cells are ATM deficient.

Applicant's arguments filed 12/1/03 have been fully considered but they are not persuasive. In the prior art, there is no indication that HeLa cells are by nature ATM deficient. Rappold et al teach use of HeLa cells (see e.g. figure 1) as control cells for the characterization of ATM activity. Gately et al (Molecular Biology of the Cell, 1998, see e.g. page 2364, column

2, last paragraph) teach detection of ATM in HeLa cells and furthermore state that upon comparison of ATM levels in a variety of cells, ATM levels in HeLa were identified as among those expressing ATM in abundance (page 2365, column 2, paragraph 1). The specification neither teaches the ATM status of HeLa cells nor that the cells are altered to become ATM deficient. Therefore, HeLa cells cannot be classified as ATM deficient.

Applicants traverse the claim rejections under 35 U.S.C. 103(a), on pages 5-6 of the amendment filed 12/1/03. Applicants argue that the presently claimed invention has unexpected and surprising results in that the process generates ATM protein in quantities that were previously unattainable. Specifically, high yields are demonstrated due to the use of a variola viral vector and in particular a vaccinia viral vector. Kastan et al provides no motivation to select vaccinia vector but rather references it as one in a list of vectors with no suggestion of an expectation of success with its use to the magnitude of the present invention. As a result, the present claims are not rendered obvious.

Applicants' arguments filed 12/1/03 have been fully considered but they are not persuasive. The prior art teaches purification of 2 μg of endogenous ATM from 300 grams of non-transfected placenta tissue (see page 3, line 9-13 of the instant specification). Smith et al (PNAS, 1999) teach the isolation of ATM from 5 μl of non-transfected HeLa cell nuclear extracts or 50 μg of protein. Western blotting and silver staining reveal that ATM constitutes 0.005% of total nuclear protein by weight (page 11136, column 2, paragraph 1). However, it is unclear how many cells were originally used or how infection of cells with vaccinia virus vector expressing ATM would affect the quantities of ATM purified. Applicants' allegations of unexpected and surprising results are directed at claims that are not commensurate in scope with

the claimed unexpected results. The comparison between the results obtained in the prior are and the instant specification is as if comparing apples and oranges. Therefore, it is not clear how unexpected the applicants results are nor can the claims be considered unobvious.

The currently rejected claims contain no implied or implicit or expressly recited limitation that the process necessarily produce quantities of ATM protein to levels that were previously unattainable or to a specific magnitude. Applicants point to the specification at page 11, line 4 to page 12, line 2 and page 20, line 10-19 as teachings that the use of a variola viral vector has been shown to produce high yields of ATM protein. These sections teach infection of HeLa cells with a vaccinia viral vector expressing ATM for the purification of 0.3-0.5 μg /μl of ATM and state that the yield is greater than 2 μg per 300 grams of tissue. L3 (ATM deficient) cells are infected with vaccinia viral vector expressing ATM for the detection of ATM in Western blot analysis and in *in vitro* kinase assays (page 9, line 8- page 10, line 2). The disclosure only teaches that yields of greater than 2 μg per 300 grams of tissue are attained when vaccinia viral vector is used. Therefore, there is no evidence that use of any viral vector other than vaccinia would provide the unexpected results asserted by applicants.

Kastan et al teach vaccinia viral vector for the production of ATM, which is the primary reference for the 103 rejections. Therefore, it is not necessary that motivation for selection of vaccinia virus be provided by the secondary references.

It is noted that applicants state that by ATM protein they are referring to the coding sequence encoded by the human ATM gene as GenBank Accession No U82828.

Conclusion

Claims 17-19 and 21 are allowed.

Claims 1-3, 5-7, 10-16 and 23-27 are rejected.

Claim 9 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (571)-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1636

GERRY LEFFERS
PRIMARY EXAMINER

February 22, 2004